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A pooled analysis of case–control studies of thyroid cancer. VI. Fish and shellfish consumption

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Abstract

Objective: To better understand the role of fish and shellfish on thyroid cancer risk, we systematically re-analyzed the original data from 13 case–control studies conducted in the US, Japan, China, and Europe.
Methods: A total of 2497 cases (2023 women, 474 men) and 4337 controls (3268 women, 1069 men) were considered. Odds ratio (OR) and corresponding 95% confidence interval (CI) were estimated for each study by logistic regression models, conditioned on age and sex, and adjusted for history of goiter, thyroid nodules or adenomas, and radiation. Combined ORs were computed as the weighted average of the estimates from each study.
Results: The ORs for the highest level of total fish consumption (three or more times per week) as compared to the lowest one (less than once per week) was above unity in Hawaii, Connecticut, Japan, Norway, Tromsø, and Vaud. Conversely, the ORs for the studies in Los Angeles, Shanghai, southeastern Sweden, Uppsala, northern Sweden, northern Italy, and Athens were below one. The pattern of risk for salt water fish and shellfish was not substantially different from that of total fish. Fish was not associated with thyroid cancer risk in all studies combined (OR = 0.99, 95% CI 0.85–1.2 for moderate, and OR = 0.88, 95% CI 0.71–1.1 for high total fish consumption), but there was a suggestion of a protective effect in endemic goiter areas (OR = 0.65, 95% CI 0.48–0.88).
Conclusion: This combined analysis indicates that relatively elevated fish consumption does not appreciably increase thyroid cancer risk, and may have a favorable influence in areas where iodine deficiency is, or was, common.

Introduction

Descriptive epidemiology, ecological studies, and animal experiments indicate that dietary iodine may be involved in thyroid carcinogenesis [1–5], although the relation between iodine intake and thyroid function is complex. Iodine deficiency influences thyroid function directly, as well as indirectly, through a reduction in the level of thyroid hormones and a consequent rise in thyroid-stimulating hormone (TSH) secretion, and has been associated with an increased incidence of goiter and thyroid cancer, particularly of the follicular and anaplastic histological types. On the other hand, iodine excess also alters thyroid gland functioning, and there are indications that it may increase specifically the risk of papillary thyroid cancer [6, 7].

Fish, especially salt water fish and shellfish, are the major natural source of iodine in the human diet, and it has been reported that in the some coastal areas a diet rich in fish and other seafood has an adverse effect on the thyroid gland [8]. Only a few analytical studies have specifically evaluated the role of iodine-rich fish and seafood on thyroid cancer risk, and their results are inconclusive [9]. A direct association with fish and shellfish consumption has been reported in two studies from the US [10, 11], in an investigation from Shanghai, China [12], and in a Norwegian case–control study [13]. No significant association emerged in three studies from northern Europe [14, 15], whereas a study on papillary thyroid cancer among women from southeastern Sweden [16], and pooled data from Italy and Switzerland [17], suggested that high intake of fish conferred significant protection against thyroid cancer. It is thus conceivable that fish may differentially affect the risk of thyroid cancer and its various histological types.

In order to provide a comprehensive picture of the possible relation between fish and thyroid cancer risk, we systematically considered this association in a pooled analysis of case–control studies of thyroid cancer [18].

Methods

The 14 studies included represent all case–control studies on thyroid cancer identified through MEDLINE searches, published between 1980 and 1997, or through personal knowledge of the authors.

Four studies were conducted in the US, including one in Los Angeles [19], one in western Washington [20], one in Hawaii [10], and one in Connecticut [11]. Two were conducted in Asia, one in Hiroshima and Nagasaki, Japan (Mabuchi, personal communication), and the other in Shanghai, China [12]. Five of the eight European studies were conducted in Scandinavian countries, three in Sweden [14–16, 21], and two in Norway [13, 15, 21], and the remaining three in northern Italy [22], the Swiss canton of Vaud [23], and Athens, Greece [24]. The study from western Washington [20] was not considered in the present analysis, since it had no information on fish intake. A detailed description of the studies included in the pooled analysis is given in a separate paper [18] and in the original study publications.

A total of 2497 cases (2023 women, 474 men) and 4337 controls (3268 women, 1069 men), providing valid data on fish intake, were included. Most of the cancers were papillary (1983, 79.4%), followed by follicular (321, 12.9%), medullary (63, 2.5%), anaplastic (17, 0.7%), and a few others of undefined histology (113, 4.5%).

The original dataset were restructured according to a uniform format, and analyzed in a standardized way. The variables considered in this combined analysis were total fish, including both salt water and fresh water fish, salt water fish and shellfish consumption. They were derived from dietary questionnaires of very different length (from 4 to 150 items) (Table 1). Six studies had a single item for total fish [13, 14, 16, 22–24], while specific information on salt water fish was collected in seven studies [10–12, 15, 19]. Ten studies also collected information on shellfish [10–12, 14–16, 19, 24]. Items for fresh water fish or other fish products were collected in a few studies, but they were not considered in the present analysis, since consumption was generally low.

The frequency of intake of each item was originally expressed in times per week or per month in four studies [10, 22–24], whereas in the others it was codified into a few categories. For our analysis, the consumption of total fish and salt water fish was *a-priori* categorized into three levels, corresponding approximately to consumption of less than once per week, one to less than three times per week, and three or more times per week. Shellfish consumption was grouped into three categories, corresponding to no consumption, twice or less per month and more than twice per month. Given the different frequency of consumption in various populations, no definition of continuous terms was possible. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were estimated for each study by conditional logistic regression models [25], using the original matching sets for matched studies, and stratifying by sex and quinquennia of age for unmatched ones. In all centers, ORs have been adjusted for history of goiter and thyroid nodules or adenomas, and history

Table 1. Details of the dietary questionnaires used in the pooled analysis of case–control studies of thyroid cancer

Study and location	Total number of food items	Items for fish (N.)	Frequency measurement	Time period of diet reporting
America – USA				
Los Angeles	5	Salt water fish (1), fresh water fish (1), shellfish (1)	5 categories	As an adult (≥20 years)
Hawaii	Over 150	Salt water fish (48), fresh water fish (2), shellfish (9)	Absolute	Usual diet
Connecticut	12	Salt water fish (1), fresh water fish (1), shellfish (1)	5 categories	Usual diet
Asia				
Japan	40	Salt water fish (4), shellfish (1), fish products (1)	8 categories	Present diet
Shanghai, China	4	Salt water fish (1), fresh water fish (1), shellfish (1)	5 categories	As an adult (≥20 years)
Europe – North				
Southeastern Sweden	8	Total fish (1), shellfish (1)	4 categories	After age 20 years
Uppsala, Sweden	32	Salt water fish (5), fresh water fish (1), shellfish (1), fish products (3)	6 categories	Usual diet before diagnosis
Northern Sweden	6	Total fish (1), shellfish (1)	4 categories	After age 20 years
Norway	15	Total fish (1)	4–7 categories	Usual diet before diagnosis
Tromsø, Norway	32	Salt water fish (7), fresh water fish (1), shellfish (1), fish products (3)	6 categories	Usual diet before diagnosis
Europe – South				
Northern Italy	24	Total fish (1)	Absolute	Habitual diet
Vaud, Switzerland	29	Total fish (1)	Absolute	Habitual diet
Athens, Greece	62	Total fish (1), shellfish (1)	Absolute	Present diet

of radiation. For Hawaii the model was conditioned also on ethnicity.

The results of the present analysis may differ somewhat from those already published because of different variable definitions and statistical models used to maintain uniformity across studies.

A common OR for the variables of interest has been computed as the weighted average of the estimates from various studies, with weight proportional to the inverse of the variance of the OR [26]. The degree of heterogeneity between study estimates has been quantified. Heterogeneity has also been evaluated in relation to the residence in endemic goiter areas (defined according to clinical knowledge and prevalence of goiter in controls [27]), and the quality of the questionnaires (classified into three groups, according to the level of detail), in order to understand whether these variables may explain, at least in part, the difference in ORs between studies. Graphs are presented displaying the ORs and the corresponding 95% CI for the highest level of consumption of total fish, salt water fish, or shellfish, as compared to the lowest one.

Table 2. Odds ratio[a] (OR) of thyroid cancer and corresponding confidence interval (CI) according to level of total fish consumption in each study

Study and location	Level of consumption			χ^2 trend (*p*-value)
	Low	Moderate	High	
America – USA				
Los Angeles				
Upper cutpoint	<1/week	<3/week		
Ca:Co	187:188	52:37	31:47	
OR, 95% CI	1[b]	1.5 (0.87–2.7)	0.66 (0.37–1.2)	0.77 (0.38)
Hawaii[c]				
Upper cutpoint	<1/week	<3/week		
Ca:Co	34:111	83:200	71:125	
OR, 95% CI	1[b]	1.2 (0.70–1.9)	1.3 (0.74–2.2)	0.74 (0.39)
Connecticut				
Upper cutpoint	<1/week	<3/week		
Ca:Co	130:239	4:21	25:24	
OR, 95% CI	1[b]	0.3 (0.08–1.1)	2.0 (1.1–3.9)	2.35 (0.13)
Asia				
Japan				
Upper cutpoint	<1/week	<4/week		
Ca:Co	7:8	173:192	185:165	
OR, 95% CI	1[b]	0.96 (0.34–2.7)	1.2 (0.40–3.4)	1.38 (0.24)
Shanghai, China				
Upper cutpoint	<1/week	<3/week		
Ca:Co	88:101	92:78	20:21	
OR, 95% CI	1[b]	1.2 (0.79–1.9)	0.93 (0.45–2.0)	0.13 (0.72)
Europe – North				
Southeastern Sweden				
Upper cutpoint	Sometimes/month	Sometimes/week		
Ca:Co	22:45	123:261	29:79	
OR, 95% CI	1[b]	0.77 (0.41–1.5)	0.46 (0.22–0.98)	4.86 (0.027)
Uppsala, Sweden				
Upper cutpoint	<4/month	<12/month		
Ca:Co	25:39	108:151	34:62	
OR, 95% CI	1[b]	1.2 (0.66–2.2)	0.85 (0.41–1.8)	0.35 (0.55)
Northern Sweden				
Upper cutpoint	Sometimes/month	Sometimes/week		
Ca:Co	31:42	107:212	33:71	
OR, 95% CI	1[b]	0.71 (0.42–1.2)	0.65 (0.34–1.2)	1.61 (0.20)
Norway				
Upper cutpoint	<4/month	<12/month		
Ca:Co	2:13	52:288	38:159	
OR, 95% CI	1[b]	1.2 (0.26–5.7)	1.6 (0.34–7.7)	1.59 (0.20)
Tromsø, Norway				
Upper cutpoint	<4/month	<12/month		
Ca:Co	6:14	31:66	43:111	
OR, 95% CI	1[b]	1.3 (0.41–4.0)	1.1 (0.34–3.2)	0.12 (0.73)
Europe – South				
Northern Italy				
Upper cutpoint	<1/week	<3/week		
Ca:Co	149:226	232:341	18:49	
OR, 95% CI	1[b]	1.0 (0.76–1.3)	0.5 (0.29–0.96)	1.63 (0.20)
Vaud, Switzerland				
Upper cutpoint	<1/week	<3/week		
Ca:Co	28:102	85:279	10:31	
OR, 95% CI	1[b]	1.0 (0.60–1.8)	1.1 (0.42–2.7)	0.03 (0.87)

Table 2. (Continued)

Study and location	Level of consumption			χ^2 trend (p-value)
	Low	Moderate	High	
Athens, Greece				
Upper cutpoint	<4/month	<12/month		
Ca:Co	37:41	64:88	8:10	
OR, 95% CI	1[b]	0.55 (0.30–1.0)	0.77 (0.25–2.4)	1.84 (0.17)

[a] Estimates from conditional logistic regression models, conditioned on age and sex, and adjusted for history of goiter and thyroid nodules or adenomas, and history of radiation.
[b] Reference category.
[c] Conditioned also on ethnicity.

Results

The association between total fish consumption and thyroid cancer risk in each study is shown in Table 2. The ORs for the highest level of consumption (three or more times per week), as compared to the lowest one (less than once per week), was above 1.0 for Hawaii, Connecticut, Japan, Norway, Tromsø, and Vaud. Conversely, the ORs for the studies from Los Angeles, Shanghai, southeastern Sweden, Uppsala, northern Sweden, northern Italy, and Athens were below one. None of the estimates was significant, however, apart from the increased risk in Connecticut and the inverse association observed in southeastern Sweden and northern Italy; a significant increased trend in risk for subsequent levels of fish consumption emerged only in southeastern Sweden. The ORs of high total fish consumption in each single study and the corresponding 95% CIs are also shown in Figure 1. Estimates from each study were broadly overlapping with those from the others.

Table 3 shows the combined ORs for all studies, for studies in endemic goiter areas, and in iodine-rich areas separately. The combined ORs for all studies were 0.99 (95% CI 0.85–1.2) for moderate and 0.88 (95% CI 0.71–1.1) for high total fish consumption, as compared to low consumption. A non-significant heterogeneity ($p = 0.16$) was found between studies, largely due to the difference in the effect of fish intake in areas of endemic goiter compared to iodine-rich areas. The corresponding ORs were in fact 0.91 (95% CI 0.75–1.1) and 0.65 (95% CI 0.48–0.88) in endemic goiter areas and 1.2 (95% CI 0.91–1.5) and 1.1 (95% CI 0.85–1.5) in iodine-rich areas. When analysis was restricted to papillary carcinoma or to women, the pattern of risk for fish and shellfish consumption was very similar, apart from a few changes in the significance of the ORs. The combined OR of papillary thyroid cancer was 0.95 for moderate and 0.84 for high total fish consumption. The corresponding ORs of thyroid cancer for women were 1.1 and 0.94. No

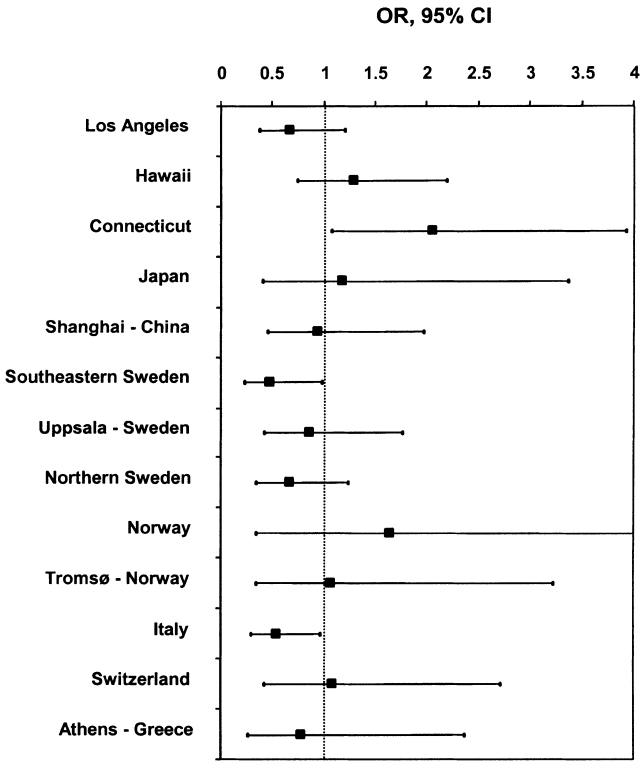

Fig. 1. Odds ratio (OR) of thyroid cancer and corresponding 95% confidence interval (CI) according to high total fish consumption by study.

significant heterogeneity was found between estimates, when studies were grouped according to the quality of their questionnaires.

Figure 2 shows the association between high salt water fish consumption and thyroid cancer risk, in seven studies. The pattern of risk for salt water fish consumption is not substantially different from that observed for total fish consumption and the results were comparable across different studies.

The ORs for high shellfish consumption in nine studies are displayed in Figure 3. Many studies showed

Table 3. Combined odds ratio[a] (OR) of thyroid cancer and corresponding confidence interval (CI) according to level of total fish consumption

	Level of consumption			
	Low	Moderate	High	*p*-trend
All studies				
OR	1[b]	0.99	0.88	0.59
95% CI		(0.85–1.2)	(0.71–1.1)	
χ^2 heterogeneity between studies (12 d.f.)		12.85, $p = 0.38$	16.76, $p = 0.16$	
Papillary carcinoma				
OR	1[b]	0.95	0.84	0.28
95% CI		(0.80–1.1)	(0.67–1.1)	
χ^2 heterogeneity between studies (12 d.f.)		15.47, $p = 0.22$	17.92, $p = 0.12$	
Women				
OR	1[b]	1.09	0.94	0.95
95% CI		(0.92–1.3)	(0.75–1.2)	
χ^2 heterogeneity between studies (12 d.f.)		7.70, $p = 0.81$	12.94, $p = 0.37$	
Studies in iodine-rich areas[c]				
OR	1[b]	1.18	1.13	0.09
95% CI		(0.91–1.5)	(0.85–1.5)	
χ^2 heterogeneity between studies (6 d.f.)		5.10, $p = 0.53$	7.02, $p = 0.32$	
Studies in endemic goiter areas[d]				
OR	1[b]	0.91	0.65	0.007
95% CI		(0.75–1.1)	(0.48–0.88)	
χ^2 heterogeneity between studies (5 d.f.)		5.19, $p = 0.39$	2.99, $p = 0.70$	
χ^2 heterogeneity between areas (1 d.f.)		2.55, $p = 0.11$	6.75, $p = 0.009$	

[a] Weighted mean of the ORs from each study.
[b] Reference category.
[c] Including studies from Los Angeles, Hawaii, Connecticut, Japan, Shanghai, Norway, and Tromsø.
[d] Including studies from southeastern Sweden, northern Sweden, Uppsala, northern Italy, Vaud, and Athens.

a direct association with thyroid cancer risk, although the risk estimates were not significant, and the CIs were very broad, due to the small number of subjects in the highest category of shellfish intake.

Combined ORs for salt water fish were 1.0 (95% CI 0.82–1.2) for moderate and 1.1 (95% CI 0.82–1.4) for high consumption, as compared to low consumption; the corresponding values for moderate and high shellfish consumption were 1.0 (95% CI 0.86–1.2) and 1.0 (95% CI 0.80–1.3), respectively.

Discussion

Our combined analysis of data from 13 case–control studies of thyroid cancer indicates that even relatively elevated fish consumption is not appreciably related to thyroid cancer risk. The combined ORs for all studies considered were, in fact, very close to unity for both fish and shellfish consumption.

The risk estimates appeared to be somewhat heterogeneous across studies, but it is difficult to say whether the differences should be considered as random variation around unity or could be attributed to different populations, study designs, and pattern of fish consumption. The heterogeneous results in various areas could also be explained in terms of the general dietary pattern of the populations under study, as well as to other lifestyle and non-nutritional factors.

The risk of thyroid cancer was systematically, although not significantly, increased in areas with iodine-rich diet, such as Hawaii, Connecticut, Japan, China, and Norway. However, fish intake was found to be significantly protective in endemic goiter areas, such as Italy, Switzerland, Sweden, and Greece, characterized, at least in the past, by frequent iodine deficiency. Thus, it is possible that the association between fish consumption and thyroid cancer risk, if any, may vary according to local iodine availability. The observation of an inverse relation between fish intake and thyroid cancer risk in endemic goiter areas indirectly supports the hypothesis that low iodine intake could increase the risk for this neoplasia [8].

In some of the studies considered, the ORs for shellfish were somewhat higher than those for fish consumption, even if the excess risk was not significant.

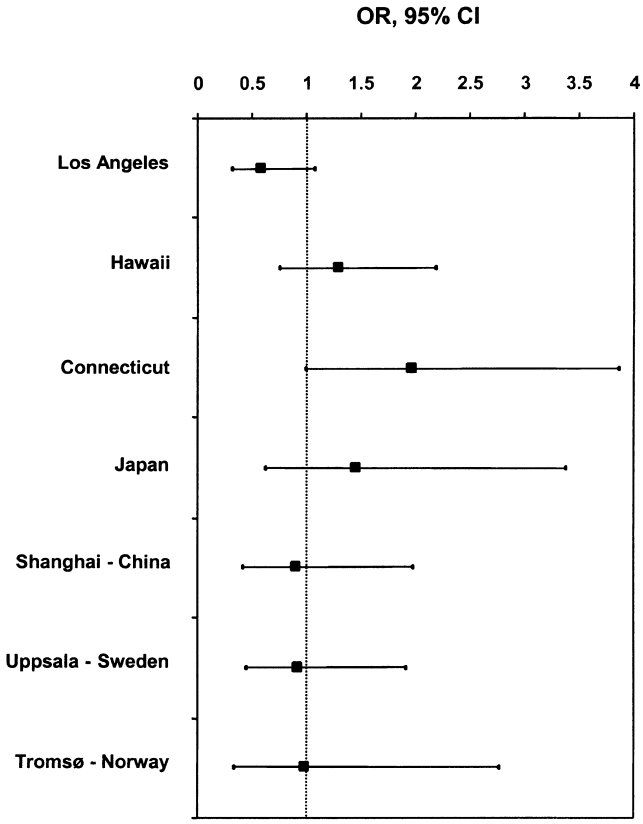

Fig. 2. Odds ratio (OR) of thyroid cancer and corresponding 95% confidence interval (CI) according to high salt water fish consumption by study.

Although it is plausible that shellfish could be associated with thyroid cancer risk, on account of the higher iodine concentration, in some studies it was not possible to clearly distinguish fish with high or low iodine content. For example, in China the most popular shellfish comes from fresh water [12], thus the item for shellfish did not include iodine-rich seafood only; in Italy and Vaud the information on shellfish was included in the only question on fish consumption in the questionnaire [17]. In general, comprehensive data on the iodine content of the most commonly consumed fish in each study area were not available from published food composition databases. Whenever possible, however, we separated salt water and fresh water fish on the assumption that fresh water fish contain substantially less iodine than do salt water fish.

Information on other significant sources of dietary iodine was not available for our investigation. Only a few studies [15, 16, 23, 24] included information on iodized salt use, and no significant association with thyroid cancer risk emerged in any of them. However, most of these datasets [15, 16, 23, 24] were from endemic goiter areas, where iodized salt had been introduced in different periods to counterbalance a diet otherwise poor in iodine.

This combined analysis had several advantages over previously published reports. It enabled the evaluation of the consistency of the results across studies conducted in various populations and using different methodologies. The use of a common definition to re-code the variables of interest also allowed removal of one of the major obstacles in the interpretation of published results from individual studies. Fixed cutpoints for the frequency of consumption of fish and shellfish were chosen for each of the studies, in an attempt to distinguish the risk of thyroid cancer for infrequent and regular fish eaters as compared to non-fish eaters. Furthermore, the ORs have been adjusted for the same confounding factors, in addition to the matching variables age and sex, including the best recognized determinants of thyroid cancer, such as history of goiter and thyroid nodules or adenomas, and history of radiation.

This analysis does have a series of limitations. Despite our efforts to ensure comparability across studies, dietary information collected in the original case–control studies was very different in terms of the level of detail of the questionnaires, items included, and

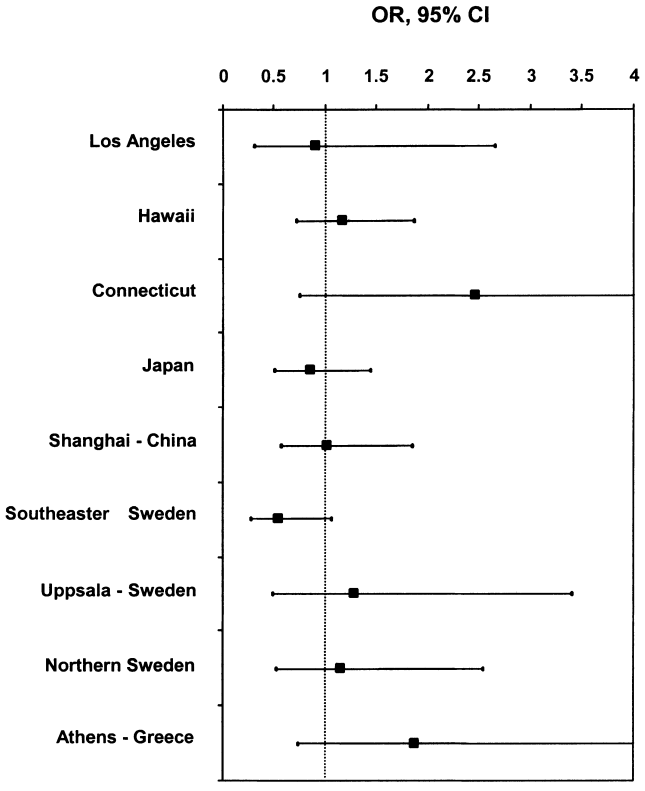

Fig. 3. Odds ratio (OR) of thyroid cancer and corresponding 95% confidence interval (CI) according to high shellfish consumption by study.

definition of frequency of measurement. Furthermore, although fish intake was an item of specific interest in most of the studies included in this collaborative re-analysis, only a few questionnaires were specifically designed to investigate dietary correlates of thyroid cancer, and only a few were tested for validity and reliability. Consequently, no allowance for total energy intake or other aspects of diet was possible [28].

Notwithstanding these limitations, it now seems possible to exclude the presence of a strong adverse effect of fish consumption on thyroid carcinogenesis, and a favorable one may be hypothesized in areas of past or current iodine deficiency.

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